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DUNNER LLP
PATENT
Customer No. 22,852
Attorney Docket No. 02481.1603-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:)
Robert BARTLETT et al.)
Application No.: 09/101,672) Group Art Unit: 1623
Filed: April 2, 2001) Examiner: E. White
For: PREPARATION CONTAINING A)
COMBINATION OF 5-METHYL-)
ISOXAZOLE-4-CARBOXYLIC)
ACID-(4-TRIFLUOROMETHYL)-)
ANILIDE AND N-(4-TRIFLUORO-)
METHYLPHENYL)-2-CYANO-)
3-HYDROXYCROTONIC ACID)
AMIDE)

Commissioner for Patents and Trademarks
Washington, DC 20231

Sir:

REPLY BRIEF UNDER 37 C.F.R. 1.193(b)(1)

Under 37 C.F.R. § 1.193(b)(1), Appellants reply to points of argument raised in the Examiner's Answer (Paper No. 32), which was mailed on December 18, 2002, in response to Appellants' Brief Under 37 C.F.R. § 1.192, filed July 17, 2002. As the U.S. Patent and Trademark Office was officially closed on February 18, 2003, this Reply Brief is timely filed on February 19, 2003. Three copies of this Reply Brief have been submitted.

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REMARKS

The Office summarizes the composition of claims 12 and 15-17 as follows:

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazole-carboxanilide ["compound 1"]; a second compound comprising the compound of formula 1 ["compound 2"]; . . . a third component comprising a pharmaceutically tolerated excipient, wherein the first component has a concentration from about 2 to about 20 mg, and the second component has a concentration from about 0.8% to about 15% of the first component.

Examiner's Answer, page 3. A similar definition, with some minor variation, is provided for method claims 20-26 and 29. *Id.*, at page 5. Claim 29 is directed to a process for preparing the inventive compounds of claim 12 into a form suitable for administration.

Appellants do not disagree with that brief summary of the invention, but provide one point of emphasis and clarification. When compound 1 is present at the highest claimed concentration (about 20 mg), compound 2 can reach a maximum concentration of only about 3 mg (about 15% of about 20 mg). Thus, the highest possible concentration of compound 2 in the claimed compositions is about 3 mg. Only very small amounts of compound 2 are ever included in the claimed composition. This is a critical point, as the art does not teach or suggest such a composition. In fact, the art teaches away from such compositions.

The Office maintains the rejection of claims 12-17, 20-26, and 29, under 35 U.S.C. § 103(a), as allegedly being unpatentable over Bartlett *et al.* (U.S. Patent No. 4,965,276). In the Examiner's Answer, the Office restates the reasoning for this rejection. Regarding each group of claims, the Office repeatedly asserts that it would be obvious to combine compounds 1 and 2 simply because they have the same utility,

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citing *In re Kerkhoven*. The Office also dismisses the specific concentrations of compounds recited in the present claims, which are not taught or suggested by Bartlett and which result in a synergistic effect, as insufficient to confer patentability because “synergism may be expected or unexpected.” Although not explicitly stated, the Office appears to assert that, in this case, the synergism is expected. Appellants disagree.

A. **Appellants Have Rebutted Any *Prima Facie* Case of Obviousness**

1. **The Present Specification Establishes Unexpected Results**

As a threshold matter, Appellants note that even if, *arguendo*, a *prima facie* case of obviousness is found, it does not conclude the patentability determination under 35 U.S.C. § 103. If a *prima facie* case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed. *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986).

In the Examiner’s Answer, the Office acknowledges Appellants’ contention that unexpected results may rebut a *prima facie* case of obviousness. However, the Office does not address the merits of Appellants’ unexpected results. Instead, the Office makes the conclusory statement that Appellants have failed to rebut a *prima facie* case of obviousness given:

[t]he evidence of record as set forth in the Bartlett et al patent with regard to the establishment of compounds . . . to treat diseases that are analogous to the diseases indicated as being treated in the instant claims, and the courts decision in *In re Kerkhoven* . . . which states that it is obvious to combine individual compositions taught to have

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the same utility to form a new composition for the very same purpose. . . .

Examiner's Answer, page 11.

Appellants first contend that the Office's reliance on *In re Kerkhoven* in this instance is misguided. *Kerkhoven* pertains to establishing a *prima facie* case of obviousness, but does not pertain to evidence submitted in rebutting the *prima facie* case once it is established. Such evidence requires reweighing the merits of the rejection. *In re Hedges, supra*.

Appellants have presented very specific evidence and a detailed discussion of the unexpected results from the originally filed specification. It is not repeated here, but is found on pages 17-19 of Appellants' Appeal Brief. As noted above, the Office claims that the unexpected results are insufficient to overcome the *prima facie* case of obviousness. Yet the Office has not provided one shred of evidence in support of its contention. Such evidence is required. *In re Soni*, 34 U.S.P.Q.2d 1684, 1688 (Fed. Cir. 1995) (holding that when an applicant demonstrates substantially improved results and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary).

In place of evidence, the Office merely cites *In re Hullmantel* [sic-Heullmantel], 324 F.2d 998 (C.C.P.A. 1963), and *Ethyl Corp. v. Ladd*, 221 F. Supp. 751 (D.C. Cir. 1963), for stating that evidence of synergism is a factor to be considered, but is not controlling, since results may be expected or unexpected. Examiner's Answer, page 12. At the outset, Appellants note that *In re Heullmantel*, decided nearly 30 years ago at the C.C.P.A., has never been cited by the Federal Circuit. *Ethyl Corp. v. Ladd* has

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never been cited by any other court. While neither of these facts eliminate the potential precedential value of the cases, they certainly call into question their relevance, given that the obviousness standard has dramatically evolved during the intervening 30 years.

More to the point, neither case is applicable to the facts here before the Board. *In re Heullmantel* involved an obviousness rejection of claims for a mixture containing a salicylate and either a prednisone or prednisolone compound. *In re Heullmantel*, 324 F.2d 998, 998-999 (C.C.P.A. 1963). The Patent Office cited three publications in support of the rejection. *Id.*, at 999-1000. The first reference, Holt *et al.*, disclosed a mixture of a salicylate and a cortisone. *Id.*, at 1000. The other two described prednisone and prednisolone as analogs of cortisone that exhibited greater potency. *Id.* The Patent Office argued that it would be obvious to substitute the cortisone with either prednisone and prednisolone and obtain the claimed invention. *Id.* In response, Heullmantel argued that the claimed combination of steroids and salicylates exhibited an unexpected synergistic result. *Id.*, at 1001.

The court disagreed, finding that Holt *et al.*, which described the mixture of salicylates and cortisone, “plainly suggest[s]” a combined therapy. *Id.*, at 1002. Moreover, Holt *et al.* reported that the combination achieved an “unusual” synergistic action. *Id.*, at 1002-1003. Thus, the court reasoned, it was well within the reach of the skilled artisan to simply substitute equivalent steroids, such as prednisone and prednisolone, in place of the cortisone used by Holt *et al.* and expect to achieve the same type of result already taught by the prior art. *Id.*, at 1003. The fact that the result

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achieved by Heullmantel was a bit better than the prior art was easily attributed to the increased potency of the prednisone and prednisolone compounds, which was disclosed in the other prior art documents. *Id.* Thus, since the "unexpected" results were already explicitly disclosed in the prior art, Heullmantel's argument failed.

The court followed similar reasoning in affirming the Board's rejection in *Ethyl Corp.* This case involved claims to a synergistic combination of a phenylenediamine compound and 2,6-di-tertiary butylphenol as antioxidants in gasoline. *Ethyl Corp. v. Ladd*, 221 F. Supp. 751, 752-753 (D.C. Cir. 1963). The Patent Office cited four references in support of the rejection. *Id.*, at 753. Three of the references disclosed the individual compounds recited in the claims, and their use as gasoline antioxidants. *Id.* The fourth reference, Walters, taught that gasoline antioxidants, including a specific phenylenediamine and tertiary butylphenol compound, worked more effectively in mixtures than they did when used separately. *Id.* Ethyl Corp. distinguished the claims from this fourth reference by noting that the specific tertiary butylphenol compound disclosed in the publication was different from the 2,6-di-tertiary butylphenol compound recited in the claims. *Id.*

The court, however, affirmed the Board's obviousness determination, finding that the fourth reference clearly taught the unexpected results obtained by mixing the antioxidants in gasoline. *Id.*, at 754. All that was left was for the skilled artisan to substitute Ethyl Corporation's claimed 2,6-di-tertiary butylphenol in place of the tertiary butylphenol disclosed in the synergistic prior art mixture of Walters. *Id.* Since the prior

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art explicitly disclosed the synergy of the mixture, the improved results reported by Appellants were to be expected. *Id.*

In both of these cases, the prior art not only disclosed the individual compounds recited in the claims, but also the unexpected synergistic results obtained by mixing the compounds. As a result, the court rejected later attempts to substitute equivalent compounds into the mixtures and claim patentability on the basis of unexpected results. Unfortunately for these late-comers, the unexpectedness had already been disclosed.

No such scenario exists in the present case. As noted above, Bartlett does not describe mixtures of the disclosed compounds. Compounds 1 and 2 are only tested individually. And, unlike *In re Heullmantel* and *Ethyl Corp.*, the cited prior art does not disclose any synergistic or unexpected results. Thus, there is no basis for the Office to suggest that Appellant's unexpected results are "expected." Appellants have made a contribution over the art in discovering the unexpected effectiveness obtained by mixing compound 1 with low amounts of compound 2.

A case more analogous to the present facts is presented in *Modine Mfg. v. U.S. Int'l Trade Comm'n*, 75 F. 3d 1545 (Fed. Cir. 1996). The claims at issue were directed to a refrigeration system having a reduced hydraulic diameter. *Id.*, at 1549. The prior art suggested that reducing the hydraulic diameter would cause an undesirable increase in pressure, yet the claimed invention achieved the opposite result. *Id.*, at 1556. Thus, Modine established that the results from reducing the hydraulic diameter were unexpected. After considering this and other factors, the court found the claims were not obvious over the prior art. *Id.*

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Similar to the prior art cited in *Modine Mfg.*, Bartlett teaches that the claimed invention is undesirable. As discussed above, Bartlett discloses that concentrations of compounds 1 and 2 below 20 mg will not work effectively. Only higher concentrations (e.g., more than 20 mg of compound 2) are disclosed as achieving any appreciable effect. The claimed invention, however, runs counter to these teachings in the prior art. As in *Modine Mfg.*, Appellants' claimed invention demonstrates that the "undesirable" works unexpectedly well.

As noted above, none of the case law cited by the Office is applicable here. Moreover, the Office's generic citation to legal precedent does not address Appellants' very detailed evidence of unexpected results. If the Office believes that Appellants' results are merely "expected," or "flow naturally from the prior art," it must establish such not by conclusory statements, but by a reasoned analysis taking into account the detailed facts showing synergistic results presented by Appellants. *In re Sang-Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (factual inquiry concerning obviousness must be thorough, searching, and based on objective evidence of record). The Office has completely failed to do so.

Appellants again reiterate that the present specification establishes unexpected synergistic results in combinations of compound 1 and small amounts of compound 2. This synergism is not taught or suggested by the cited prior art. And the claims are commensurate in scope with the concentrations for which synergy has been clearly demonstrated. Accordingly, Appellants have rebutted any alleged *prima facie* case of obviousness and respectfully request that the obviousness rejections be reversed.

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2. Bartlett Teaches Away from the Claimed Invention

Appellants also contend that the rejection has been successfully rebutted because the art teaches away from the claimed invention in a material respect.

The Office summarizes Appellants' argument concerning teaching away as follows:

the higher concentrations disclosed for compound 1 and compound 2 in the Bartlett et al patent is evidence that Bartlett et al teaches away from the presently claimed invention.

Examiner's Answer, page 11. Again, the Office understates Appellants' position and mischaracterizes Bartlett. Not only does Bartlett teach higher concentrations for compound 1 and 2, but also that lower concentrations of these compounds (as claimed by Appellants) do not work effectively. Thus, Bartlett's teachings lead one of skill in the art along a path that clearly diverges and leads away from the presently claimed invention. *Monarch Knitting Machinery Corp. v. Sulzer Morat Gmbh*, 139 F.3d 877, 885, 45 U.S.P.Q.2d 1977, 1985 (Fed. Cir. 1998) (quoting *In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q. 2d 1130, 1131 (Fed. Cir. 1994)). To emphasize this point and fully address the Office's position on the matter, relevant portions of Appellants' arguments are summarized below.

In Table 1, Bartlett discloses that 5 and 10 mg/kg of compound 1 have almost zero effect (less than 5%). In fact, 28 mg/kg of compound 1 was required to achieve any appreciable biological effect. In Table 2, both 5 and 10 mg/kg of compound 1 again show less than a 5% effect. With respect to compound 2, Bartlett only tests concentrations of 20 or 30 mg/kg (See Table 2). At 20 mg, compound 2 achieved a

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33% reduction in disease severity. At 30 mg of compound 2, a 56% reduction is reported. No lower concentrations of compound 2 are ever described.

Bartlett teaches that as the concentration of compounds 1 or 2 are increased, the compositions containing the individual compounds are much more effective. Thus, the skilled artisan would be led to use concentrations of compound 1 above 20 mg, and compound 2 above 30 mg, in order to achieve any effective result. This clearly teaches away from using a minuscule 3 mg of compound 2, which is the highest amount claimed by Appellants. To do so, according to Bartlett, would invite a worse result than the 33% reduction achieved with nearly 7 times more of compound 2 (20 mg). Thus, the skilled artisan would begin with a concentration of compound 2 that is no lower than the least effective amount (*i.e.*, 20-30 mg of compound 2) and work up to higher concentrations to achieve better results. Thus, Bartlett teaches away from the present claims.

The Office contends that this argument is not persuasive because:

the concentrations presented for compounds 1 and 2 in the Bartlett et al patent are based on compositions comprising only compound 1 or compound 2 in the composition, not a composition comprising both compounds 1 and 2 in a solid composition together.

Examiner's Answer, page 11. This reasoning merely points out the deficiencies in Bartlett, not the claimed invention. Bartlett does not provide any teaching to use the two compounds together, nor to use them in any of the ranges claimed by Appellants. Quite to the contrary, Bartlett's own teachings establish that the lower concentrations claimed by Appellants would not work.

Undeterred by this absence of Bartlett's teachings, the Office seems to fill the void with speculation that lower concentrations might be attempted in a combination of

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the two compounds. It is not clear how the Office arrived at this conclusion, as no discussion or other evidence is provided. What the Office has proposed requires one of skill in the art to select a poorly effective amount of compound 1 (20 mg) and combine it with an amount of compound 2 that is not even mentioned in the cited reference, unlikely to have any effect at all, or at best, have a completely unknown effect. The Office's contentions simply run counter to Bartlett's own teachings.

Appellants have presented actual evidence from Bartlett showing that the lower concentrations of compounds 1 and 2 should not work. The skilled artisan, following the teachings of Bartlett, would thus be required to select higher concentrations of compounds 1 or 2 (e.g., the preferred range of 50 to 100 mg) to achieve an effective result. Thus, the reference teaches away from the presently claimed compositions, which are limited to only the lower concentrations.

Accordingly, Appellants have rebutted any alleged *prima facie* case of obviousness and respectfully request that the obviousness rejections be reversed.

B. The Office Has Failed to Establish a *Prima Facie* Case of Obviousness

1. Bartlett Does Not Teach All of the Elements of the Claimed Invention

As noted above, the present claims are directed to combinations of compounds 1 and 2, wherein compound 2 is present at a concentration of about 0.8% to about 15% of the concentration of compound 1. Compound 1 may be present from about 2 mg to about 20 mg. As a result, the maximum concentration of compound 2 in the combination is about 3 mg (i.e., about 15% of about 20 mg).

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Bartlett does not teach or suggest any concentrations of compound 2 that fall below, or even close to, this amount. Rather, Bartlett describes only significantly higher concentrations of compounds 1 or 2. For example, Bartlett teaches that 20 mg of compound 2 exhibited rather poor activity, while 30 mg of compound 2 was more active. Bartlett, column 4, Table 2, lines 47-48. Bartlett also indicates that compounds 1 or 2 can be present at 10 to 200 mg, but preferably 50 to 100 mg. Bartlett, column 6, lines 31-32. Accordingly, Appellants contend that the prior art cited by the Office fails to teach or suggest each element of the present claims (*i.e.*, a mixture containing 3 mg or less of compound 2). Thus, the Office has failed to establish a *prima facie* case of obviousness.

Despite this clear absence of teachings in Bartlett, the Office insists that Bartlett discloses all the elements of the claim and again rejects Appellants' argument because:

the limitation of compound 2 to only 10 mg is based on compound 2 being in a dosage unit without the presence of compound 1 as part of the composition. The foundation of the rejection of the claims over the Bartlett et al patent is based on a composition comprising both compound 1 and 2 in the composition.

Examiner's Answer, page 9.

Appellants contend that this reasoning does not account for the deficiencies in Bartlett. As acknowledged by the Office, “[i]t is not clearly stated in the Bartlett et al patent that compounds 1 and 2 have been combined together to form a composition.”

Examiner's Answer, pages 3-4. Even if, as asserted by the Office, Bartlett suggests that the combination of compounds 1 and 2 could have been attempted, how does Bartlett arrive at a composition containing only 3 mg or less of compound 2?

Everything in Bartlett suggests using 20 mg, 30 mg, or even higher amounts of

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compound 2 in order to achieve a positive result. There is no teaching or suggestion of the specific lower amounts in the range claimed by Appellants.

Moreover, the position becomes ultimately untenable in view of the prosecution history, where the Office has already admitted that Bartlett does not teach the ranges recited in the claims. See Appeal Brief, page 6; Office Action mailed December 6, 1999, page 4.

As Bartlett does not teach all of the claim elements, Appellants contend that the Office has failed to establish a *prima facie* case of obviousness. Accordingly, Appellants request that the rejection be reversed.

2. There is No Motivation to Modify Bartlett to Derive the Claimed Invention

Appellants also contend that the Office has failed to establish a *prima facie* case of obviousness because there is no motivation to make the proposed combination, or to do so in the amounts recited in the claims.

As motivation to make the combination of compounds 1 and 2, the Office restates its position in view of *In re Kerkhoven*:

it is obvious to combine individual compositions taught to have the same utility to form a new composition for the same purpose, which is what Appellants have done. Thus, the motivation to modify the Bartlett et al patent has been established.

Examiner's Answer, page 10. The Office also summarizes two pages of Appellants' arguments concerning motivation as, "basically setting forth that the Bartlett et al patent teaches higher concentrations of compounds 1 and 2 being necessary to achieve a desired biological effect." Examiner's Answer, page 10. The Office rejects this argument, repeating its contention that "the concentration for compounds 1 and 2 that is

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presented in the Bartlett et al patent are based on compounds 1 and 2 in separate compositions." Examiner's Answer, page 10.

As discussed above, Appellants agree that Bartlett does not teach any concentrations of compounds 1 or 2 for use together in a single composition. The concentrations presented by Bartlett are only for use in compositions containing a single compound. And these concentrations are significantly higher than any concentration claimed by Appellants. To support the Office's position, Bartlett must suggest a combination of elements in the precise manner defined by Appellants claims. Yet Bartlett's teachings clearly suggest more efficacious results are obtained from using higher, not lower, concentrations of both compounds. Consequently, one of skill in the art would be motivated to use only higher concentrations of both compounds 1 and 2, even when used in combination. There is no motivation to use lower amounts.

Appellants reiterate their contention that there is no motivation to modify Bartlett to obtain the concentrations of compounds 1 and 2 recited in the claims. Accordingly, Appellants request that the rejection be reversed.

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CONCLUSION

In view of the foregoing, Appellants submit that the rejection of pending claims 12, 15-17, 20-26, and 29, as obvious over Bartlett is in error and should be reversed.

Respectfully submitted,

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